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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,185	11/19/2003	Shripad S. Bhagwat	10624-143-999	9314

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
03/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,185	BHAGWAT ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,8,10-13 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 7, 8, 10-13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/13/2009 has been entered.

Response to Arguments

Currently, claims 1, 3, 7-8, 10-13 and 17 are pending and are under examination herein.

Applicants present arguments over the 35 USC 112 first paragraph rejection regarding lack of enablement that the claims as now pending are not directed to the treatment of all cancers but are directed to a focused subset of cancers that are treatable by the inhibition of JNK and at least one other protein kinase. Applicants further argue that the claims are not directed to every modulator of JNK activity but recite a focused class of chemical compounds with a well-defined core structure. Applicants feel that the application is enabled because the specification teaches compounds that have activity against multiple kinases, provides assays for measuring the activity of compounds against numerous kinases and further provides a nexus

between kinase inhibition and the treatment of cancer. Applicants argue that experimentation is not undue because it is complex, time consuming or expensive.

The Applicants have amended the claims to focus on cancers treatable by inhibition of JNK and at least one other protein kinase and this amendment is noted. Further, Applicants have taught various assays for determining JNK activity in Example 435 of the specification and subsequently teach which of the many compounds that are taught with the core structure as taught by the formula in claim 1 have activity in JNK assays in Example 436. However, there is no teaching that the various compounds that showed activity in the JNK assays would effectively treat cancers that are treatable by inhibition of JNK and at least one other protein kinase. Regarding the above arguments, the Examiner will focus on the MPEP § 2164.

In particular, the MPEP contains a discussion regarding the correlation between in vitro and in vivo assays. It is specifically stated that "An in vitro or in vivo animal model example in the specification, in effect, constitutes a working example if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples". Keeping in mind that if the state of the prior art teaches that a particular model correlates to a specific condition then it does not have to be specifically taught in the specification. However, this is not the case in the present application. Applicants assert that they have provided a nexus between kinase inhibition and the treatment of cancer; however, there is only a discussion provided teaching that protein kinases are involved in most cellular processes and that cellular processes are involved in many disease states including

cancer. It is further discussed that the JNK pathway may play a role in lung cancer but does not specify any other types of cancers. The specification further goes on to teach that indazole compounds are useful in treating a variety of diseases including cancer, and list a laundry list of different types of cancers (of which it is not indicated which ones are associated with JNK inhibition).

Applicants supplied articles to validate the argument that there is a correlation between in vitro and in vivo applications because there is a role of JNK in many types of cancers. The Manning references elude to potential involvement of JNK in cancers but there is no definitive role discussed. As a matter of fact, Manning teaches that there may be a role for JNK in metastasis suppression however a direct test of the hypothesis in a reliable animal model of metastasis would confirm the hypothesis (see page 561, last paragraph). Further Manning teaches that JNK may play more than one role in tumour development which may be to promote or inhibit tumor development so there needs to be a deeper understanding of the role of JNK in tumors. Therefore this reference does not provide a nexus that inhibiting JNK will treat cancer. Further, as discussed previously, Force et al. teaches that though compounds may predict activity in the cell by in vitro assays, this may not be the case in vivo. Therefore it would be obvious that one would need to do preclinical analysis to determine activity of the compound.

Regarding the argument that experimentation is not undue because it is complex, time consuming or expensive, Applicants refer to *In re Bundy* and state that the Courts held that claims can be enabled notwithstanding the absence of examples of dosages

for human use or animal tests. However the facts in the *In re Bundy* case are different in that the claims in that case were drawn to analogs of naturally occurring prostaglandins and were known to have certain pharmacological properties and possess similar activity to known E-type prostaglandins. However, in the instant case, the Applicant is taking a class of compounds and asserting that they will treat cancer via inhibition of JNK and another protein kinase without indication of how this can be accomplished; therefore, this would amount to undue experimentation.

Applicant's arguments over the 35 USC 112 rejection for scope of enablement for treating all cancers have been fully considered. Applicants argue that the amendments to the claims limit the amount of cancers to a subset. This argument is not found persuasive because this may involve a vast array of cancers, such as those listed on page 40 of the specification. A treatment for breast cancer, for example, does not necessarily mean that the same compound will treat prostate cancer. Therefore, this claim is still deemed broad and the rejection is maintained.

As the Double Patenting rejections are not the sole rejections, they are being maintained and are given below for Applicant's convenience.

Upon further consideration, the 35 USC 112 first paragraph rejection over total lack of enablement is being withdrawn and a new 35 USC 112 first paragraph rejection is being added. Please see the modified rejections given below due to Applicants amendments to the claims.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7-8, 10-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific compounds inhibiting JNK2, does not reasonably provide enablement for treating cancer treatable by the inhibition of JNK and at least on other protein kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims are drawn to a method for treating cancer treatable by the inhibition of JNK and at least one other protein kinase comprising inhibiting the

activity of JNK and at least one other protein kinase comprising administering to a patient having a cancer treatable by the inhibition of JNK and at least one other protein kinase an effective amount of the compound having the structure in claim 1.

2) The presence or absence of working examples and the amount of direction or guidance presented: In the instant case, working examples are presented for measuring the activity of the compounds of the invention in various assays, such as JNK2 assay, JNK3 assay, Jurkat T-cell 11-2 Production Assay, rat in vivo LPS-induced TNF-α Production assay and various other assays (see Examples 435-509). In particular, Example 435 teaches JNK assays and Example 436 teaches specific compounds of the invention that inhibit JNK2. However, there is no data exemplifying treatment of any type of cancer with the compounds of the invention or any teaching that inhibition of JNK2 will treat cancer.

The extent of the studies of the present invention is to determine the activity of the various indazole compounds of the invention in treating cancer treatable by the inhibition of JNK and at least one other protein kinase. The determination of a particular claimed compound in the treatment of any type of cancer requires the synthesis of the compound, formulation into a suitable dosage form, and testing in a known assay that is correlated with clinical efficacy. Applicants state on pages 40-42 that the compounds of the invention are useful in treating cancer and list various cancers that can be treated. However, there are no further examples exemplifying the effectiveness of the compounds in an animal model of any particular cancer with no effective dose range

being determined in the treatment of cancer. Furthermore, there is no teaching of which cancers are treatable by JNK inhibition or other protein kinase inhibition.

There is no correlation presented or found in the art that makes the conclusion that inhibition of JNK2 in an *in vitro* assay automatically leads to the treatment of cancer. The issue in *Ex parte Balzarini* 21 USPQ2d 1892 concerned HIV treatment and the Board of Patent Appeals and Interferences wrote "while the *in vitro* testing performed on these anti-viral compound appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predictive of *in vivo* efficacy". Furthermore, the issue in *Fujikawa v. Wattanasin* 39 USPQ2d 1895 was adequacy of *in vitro* testing of inhibitors of cholesterol biosynthesis and U.S. Court of Appeals Federal Circuit wrote, "*in vitro* results, in combination with a known correlation between such *in vitro* results and *in vivo* activity, may be sufficient to establish practical utility". A working example is lacking in the present invention in which *in vivo* experiments show that the compounds would effectively treat cancer or that the *in vitro* assays necessarily lead to the conclusion that the compounds that inhibit JNK2 will treat cancer.

3) The state of the prior art: The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art

is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual" or not provided in the specification, *Ex parte Jovanovics*, 211 USPQ 907, *In re Langer*, 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

It is art recognized that a perturbation of protein tyrosine kinase (PTK) activity results in a variety of diseases, including cancer (see Al-Obeidi et al., Oncogene (2000) 19, 5690-5701). In the Introduction of this paper, it is stated that many PTK's have been implicated in human cancer and give examples of some specific PTK's that are implicated in different types of cancer. Al-Obeidi et al. goes on to discuss the approaches to the development of inhibitors and discusses compounds that have been tested in pre-clinical and clinical studies. Al-Obeidi et al. discusses that inhibitors of some PTK's may be useful for the treatment of a number of diseases and that a large number of PTK inhibitors have been developed and that several are undergoing clinical trials. Al-Obeidi et al. conclude that it is likely that several clinically useful PTK inhibitors will be on the market within the next decade, making it evident that not all of the PTK

inhibitors that will be synthesized will necessarily be effective in clinical situations and should be tested. Further there is no teaching that JNK2 is the target of specific cancers nor that inhibition of JNK2 is the treatment method for any type of cancer.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification as to what cancers are treatable by JNK2 inhibtion, indazole compounds that have *in vivo* activity at JNK2 or any data (either *in vitro* or *in vivo*) that correlate inhibition of JNK2 with the treatment of cancer. One would have to determine a useful model that correlates with clinical efficacy, a dosage range would need to be determined as well as a route of administration. Further, if any of the above failed, then the artisan would have to start over again in an effort to determine the suitable methods, dosage ranges and routes of administration in which to determine if the compounds will work to treat cancer.

Claims 1, 3, 7-8, 10-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of JNK2 in *in vitro* assays by various indazole compounds of the structure in claim 1, does not reasonably provide enablement for the treatment of any cancer with the indazole compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims are drawn to a method for treating cancer treatable by the inhibition of JNK and at least one other protein kinase comprising inhibiting the activity of JNK and at least one other protein kinase comprising administering to a

patient having cancer treatable by the inhibition of JNK and at least one other protein kinase an effective amount of a compound having the structure in claim 1.

2) The presence or absence of working examples and the amount of direction or guidance presented: In the instant case, working examples are presented for measuring the activity of the compounds of the invention in *in vitro* assays of inhibition of JNK2. These assays verified the ability of the compounds to inhibit JNK2 and their corresponding IC50 value. However, there is no data exemplifying treating any type of cancer with the compounds of the invention. There is no data presented in accepted animal models of various types of cancer suggesting that indazole compounds would show clinical efficacy in treating all cancers.

3) The state of the prior art: The state of the art for the treatment of various types of cancer is high.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification showing that any

type of cancers would be treated following administration of indazole compounds. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claims 1, 3, 7-8, 10-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, there is no teaching of administration of any of the various indazole compounds to a patient for the treatment of any type of cancer. Furthermore, there is no teaching as to what cancers are treatable by JNK inhibition and at least one other protein kinase or a compound that inhibits JNK and at least one other protein kinase. The only data presented in the specification is a showing of certain compounds that inhibit JNK *in vitro*, but there is no written description that the compounds have been administered to a patient having cancer or an experimental model of this.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 13 and 17 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 9-10 of copending Application No. 11/512,836. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a method for treating disease (cancer) comprising administration of an indazole compound (3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole). The claims of application 11/512,836 are drawn to a method for treating chronic lymphocytic leukemia comprising administration of 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. The applications are obvious over the other in that they both involved treatment of a cancer with indazole compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 13 and 17 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/376,786. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a method for treating disease (cancer) comprising administration of an indazole compound (3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole). The claims of application 11/376,786 are drawn to a method for treating acute myelogenous leukemia comprising administration of 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. The applications are obvious over the other in that they both involved treatment of a cancer with indazole compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617